REMARKS

Claims 1 – 3, 23 – 25 and 50 - 51 are pending in the application. Claims 4 – 22 and 25 – 51 have been cancelled as being drawn to non-elected subject matter. Claims 1 and 2 have been amended. New claim 52 has been added.

No new matter has been added by virtue of these amendments; support therefore can be found in throughout the specification and original claims of the application.

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Objections

Drawings

The Examiner argues that the drawings filed on 5/05/2005 are objected to under 37 CFR 1.83(a) because "they fail to show the specific details as disclosed in the brief description on pages 4 – 7 of the specification." (Office Action, p.2).

Applicants are submitting replacement drawings with the present response.

Rejection of Claims 1 - 3 and 23 – 25 Under 35 USC 112, First Paragraph

Claims 1 – 3 have been rejected under 35 USC 112, first paragraph for allegedly failing to comply with the written description requirement. The Examiner argues that the claims contain subject matter that was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

As pointed out by the Examiner, the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by "...**disclosure of relevant identifying characteristics, i.e., structure** or other physical and/or chemical properties, by functional characteristics **coupled with a known or**

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disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus."

The claims are drawn to method of killing a tumor cell using a genus of siRNAs that are at least 95% identical to SEQ ID NO: 4, and that are specific for a DNA repair protein.

The specification teaches actual reduction to practice of siRNAs that encode a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4. As pointed out by the Examiner, Figure 15 depicts the sequences of the oligonucleotides used to construct the ATM-2 siRNA-encoding nucleic acid molecules, including SEQ ID NO: 4. The specification teaches using the siRNA constructs of the instant invention for down-regulation of DNA repair proteins, including ATM, for example starting at paragraph [0138] and further teaches siRNA silencing of repair proteins using the siRNAs taught in the instant invention to render tumor cells sensitive to DNA-damaging Agents [0140]. There are certain art-recognized correlations between siRNA function and the structure of the target that would aid the selection of those fragments having antisense activity, and, accordingly, the structure of all possible siRNAs that are at least 95% identical to SEQ ID NO: 4 can be predicted from SEQ ID NO: 4.

Example 14 of the Written Description Guidelines Training Materials illustrates the application of the written description requirement to the following generic claim:

> A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A → B.

Under the Training Materials, a generic claim similar to Example 14 would be adequately described under Section 112, ¶ 1, because (1) "[t]he single species disclosed is *representative of the genus* because all members have at least 95% structural identity with the reference compound," and (2) because of the limitation requiring the stated compounds to catalyze the reaction of A → B. See Training Materials at 54. (Emphasis added).

Likewise, the instant claims are directed to siRNA is encoded by a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4 and at least one DNA-

damaging agent and wherein the siRNA and the at least one DNA damaging agent kill a tumor cell.

Accordingly, based on the Guidelines, the instant claims satisfy the written description requirement and, therefore, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection

Given the high level of skill in the siRNA art, those of ordinary skill in the art would consider the applicant to have been in possession of the entire breadth of the claimed genus of siRNAs based on the teachings of the disclosure.

Applicants respectfully request that the rejection be withdrawn.

Rejection of Claims 1 - 3 and 23 – 25 Under 35 USC 112, First Paragraph

The rejection of claims 1 - 3 and 23 – 25 under 35 USC 112, first paragraph for allegedly failing to comply with the enablement requirement has been maintained by the Examiner. The Examiner argues that the claims, while being enabling for a method of killing a tumor cell in vitro comprising contacting the cell in vitro with a small inhibitory RNA specific for a DNA repair protein and at least one DNA-damaging agent, does not reasonably provide enablement for a method of killing a tumor cell comprising contacting the cell in vivo with a siRNA specific for a DNA repair protein and at least one DNA-damaging agent. Applicants respectfully traverse this rejection.

The instant claims recite a method of killing a tumor cell comprising contacting the cell with at least one small inhibitory RNA (siRNA), wherein the siRNA is encoded by a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4 and at least one DNA-damaging agent, wherein the siRNA and DNA damaging agent kill a tumor cell. The claims also recite a method of treating a subject having cancer comprising administering to the subject a therapeutically effective amount of at least one small inhibitory RNA (siRNA) and a therapeutically effective amount of at least one DNA-damaging agent.

The specification provides detailed teachings regarding the claimed methods to enable the claimed invention.

Applicants point out that at paragraph [0078], the specification teaches that with respect to the methods of the invention:

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> target cancer cells (i.e., neoplastic, proliferative cells) are contacted with an appropriate siRNA vector described herein (preferably in the form of an adenovirus) such that the vector enters the cell and expression of the siRNA is induced. The target cancer cells are further exposed to a DNA-damaging agent (e.g., radiation and/or chemotherapeutic agent(s)).

The specification then teaches step by step how methods of the invention would be carried out.

First, the specification teaches that the siRNAs of the invention can be targeted to any DNA repair protein. Applicants direct the Examiner to paragraph [0081] of the disclosure that teaches the target and possible sequences of the siRNAs:

> The siRNA may be targeted to any DNA repair protein known to participate in DNA repair pathways activated in response to DNA-damaging agents, including, but not limited to, ATM, ATR, and/or DNA-PKcs. The siRNA may target any region in the target mRNA, and may be encoded, for example, by one ore more of the nucleic acid sequences set forth in SEQ ID NO:1, 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26, 28, 29, 30, 31, 32, 33, 34, 35, or 36. The methods of the invention may use siRNA targeting a single DNA repair protein, or may use a mixture of siRNA targeting more than one DNA repair protein. For example, in a preferred embodiment, the methods of the invention use siRNA targeting one, two, three or more DNA repair proteins.

Next, beginning at paragraph [0094], the specification clearly teaches how to isolate nucleic acids that encode the siRNAs used in the method of the invention. The specification teaches at [0096] that standard techniques, e.g. "techniques for isolating mRNA, purifying and analyzing nucleic acids, methods for making recombinant vector DNA" are well known in the field. At paragraphs [0098] – [0100] the specification teaches how to construct nucleic acid molecules of the invention, how to isolate the nucleic acid molecules using synthetic oligonucleotide primers designed based upon the sequences disclosed, and how to produce the siRNAs of the invention by inserting a double-stranded DNA molecule that encodes the siRNA into an expression vector.

Additionally, the specification teaches how to deliver the adenoviral vectors to

the target cell. For example, at [0091], the specification teaches that "adenoviral vectors may be delivered to the target cell in a variety of ways, including, but not limited to, liposomes, general transfection methods that are well known in the art (such as calcium phosphate precipitation or electroporation), direct injection, and intravenous infusion."

The specification sets forth at [0086] – [0093] dosage and administration of the adenoviral vectors to the target cell. At [0086], the specification describes dosage levels and schedules. The specification teaches at [0088] tumor cells that can be targeted by the methods of the invention:

> The methods of the invention are intended to be used for any type of tumor, cancer, and/or neoplasm, including, but not limited to, those derived from prostate, colon, breast, lung, brain, skin, ovary, pancreas, liver, stomach, bladder, bone, testicle, uterus, adipose tissue, throat, kidney, tongue, pituitary gland, thyroid, nerve, lymphoid tissue, eye, and/or cervix. Additionally, the methods of the invention are intended to be used for tumors which may be a mixture of more than one cell type, as well as for metastasized tumors which are originally derived from one cell type, but have migrated to a different part of the body.

Accordingly, the specification as filed enables one of skill in the art to make and/or use the invention as claimed. Applicants respectfully request that the rejection be withdrawn.

Rejection of Claim 1 Under 35 USC 103(a)

The rejection of claim 1 under 35 U.S.C. § 103(a) as being unpatentable over Fan et al. (Cancer Gene Therapy 2000, Vol. 7, No. 10: 1307 – 1314), in view of Hammond et al. and Tuschl et al. (WO 02/44321) has been maintained by the Examiner. Applicants respectfully traverse the rejection.

Claim 1 recites a method of killing a tumor cell comprising contacting the cell with at least one small inhibitory RNA (siRNA), wherein the siRNA is encoded by a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4 and at least one DNA-damaging agent, wherein the siRNA and DNA damaging agent kill a tumor cell.

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The Fan et al. reference fails to teach or suggest all the elements of the instant invention. In particular, the Fan reference does not teach or suggest contacting the cell with at least one small inhibitory RNA (siRNA), wherein the siRNA is encoded by a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4 and at least one DNA-damaging agent, wherein the siRNA and DNA damaging agent kill a tumor cell. Nowhere in the Fan reference is there teaching or suggestion of SEQ ID NO: 4 or a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4.

The Examiner argues that the Fan reference teaches generation of an antisense molecule from the transcriptional start domain of the human ATM gene having nucleotides 188 to 445 which comprises nucleotides 395 to 445 of SEQ ID NO: 4. (Office Action, p.7). The Fan reference teaches that cDNA fragments containing either the translational start domain (188 – 445 bp), the PI-3K domain (8167 – 8854) or both of these domains of the ATM gene were cloned in an antisense orientation from the CMV promoter in an adenovirus plasmid, and then cotransfected into cells. Nowhere does the Fan reference teach or suggest **siRNA that is encoded by a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4** as taught by the instant claims. All siRNAs that are complementary to the ATM target mRNA sequence will not have gene silencing effects. The claims are directed to specific siRNA molecules that are encoded by nucleic acid molecules that are at least 95% identical to SEQ ID NO: 4 and have gene silencing activity. It is not known if any siRNA to any target sequence in the ATM gene between nucleotides 188 – 445 would have gene silencing effects. Nowhere does the Fan reference teach or suggest use of siRNA silencing and nowhere does Fan teach or suggest silencing of the nucleic acids encompassed by SEQ ID NO: 4 or a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 4.

Neither of the Hammond nor the Tuschl references cure the defects of the Fan reference. Nowhere in either of the Hammond or the Tuschl references is there teaching or suggestion of the specific sequence set forth as SEQ ID NO:4. Therefore, the teachings of the cited art, when combined, do not result in the claimed invention.

Accordingly, Applicants request that the rejection be withdrawn.

Early consideration and allowance of the application are earnestly solicited.

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Respectfully submitted,

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